Supporting Information: Spectroelectrochemical and Computational Studies of Tetrahydrocannabinol (THC) and carboxy-Tetrahydrocannabinol (THC-COOH)

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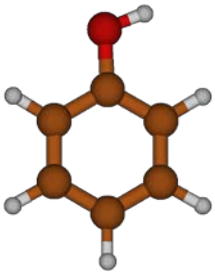
Computational Studies - Methodology

A series of smaller model molecules were calculated first. **Phenol** (C_s #1) prefers to have its hydroxyl group in the plane of the benzene ring, with the higher energy alternative (C_s #2) being the conformational transition state (~12 kJ/mol) connecting the two isoenergetic forms. **Dimethylbenzopyranol** prefers to be nonplanar (C_1) in one of two forms, with the form with the hydroxo group pointing away from the pyran ring (C_1 #1) preferred by 5-8 kJ/mol. The planar form (C_s #1) is the transition state (~2.5 kJ/mol) connecting the two stereoisomers. **Dimethyldihydrobenzopyranol** is also nonplanar (C_1) in one of two forms, with the form with the hydroxo group pointing away from the dihydropyran ring (C_1 #1) preferred by 5-8 kJ/mol. The planar C_s forms are second-order saddle points. ***meta*-Pentylphenol** can have one of four C_s forms, differing in the hydroxyl and pentyl orientation with little energetic difference between them (1 kJ/mol). Scans about the dihedral angle connecting the ring to the pentyl chain indicate that nonplanar C_1 form would be preferred. The two C_1 structures thus derived are nearly isoenergetic, but lower than the C_s forms by 5-8 kJ/mol. These calculations establish the preferred conformation of the hydroxyl group and the pentyl side-chain. For the larger molecules that follow, none of the MP2 calculations were attempted for computational expediency. Two low-energy forms (C_1 #1, #2) of **pentyldimethylbenzopyranol** were found to be essentially isoenergetic (0.05 kJ/mol), and the same holds true of **pentyldimethyldihydrobenzopyranol** (0.1 kJ/mol). The barrier to their interconversion via a more planar benzo(dihydro)pyranol ring would be low. Next, the ring systems of several cannabinoids were constructed (without the pentyl groups). **Cannabinol (no pentyl)** C_s #1 and C_1 #1 differ in energy by 12-13 kJ/mol. **7,8-dihydrocannabinol (no pentyl)** and **12,13-dihydrocannabinol (no pentyl)** have no symmetry, and the latter is more stable by 30-40 kJ/mol. **7,8,12,13-tetrahydrocannabinol (no pentyl)** also has no symmetry

phenol C_s #1



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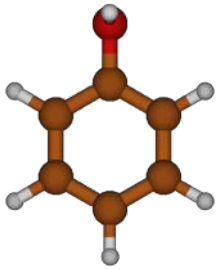

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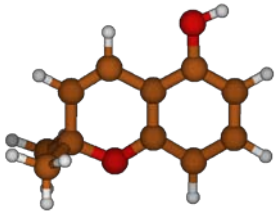

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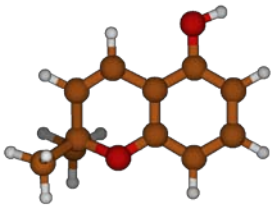

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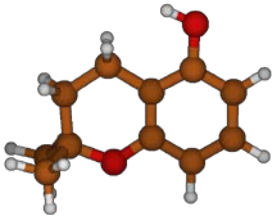

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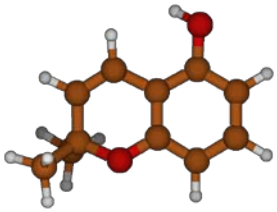

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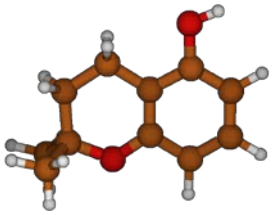

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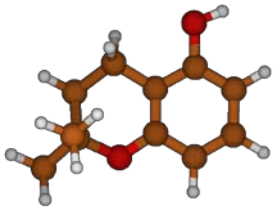

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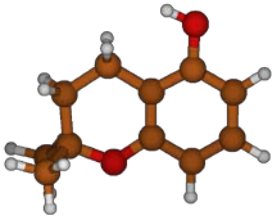

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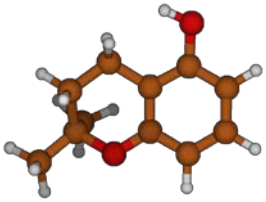

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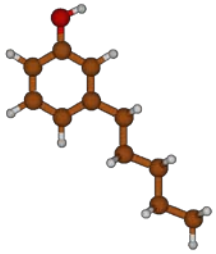

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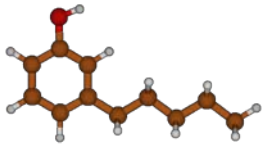

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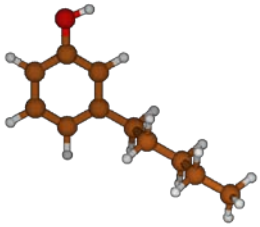

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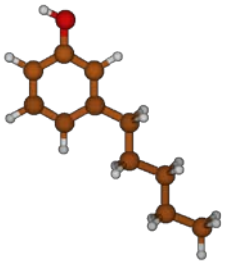

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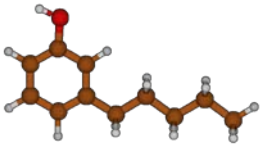

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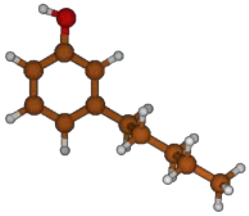

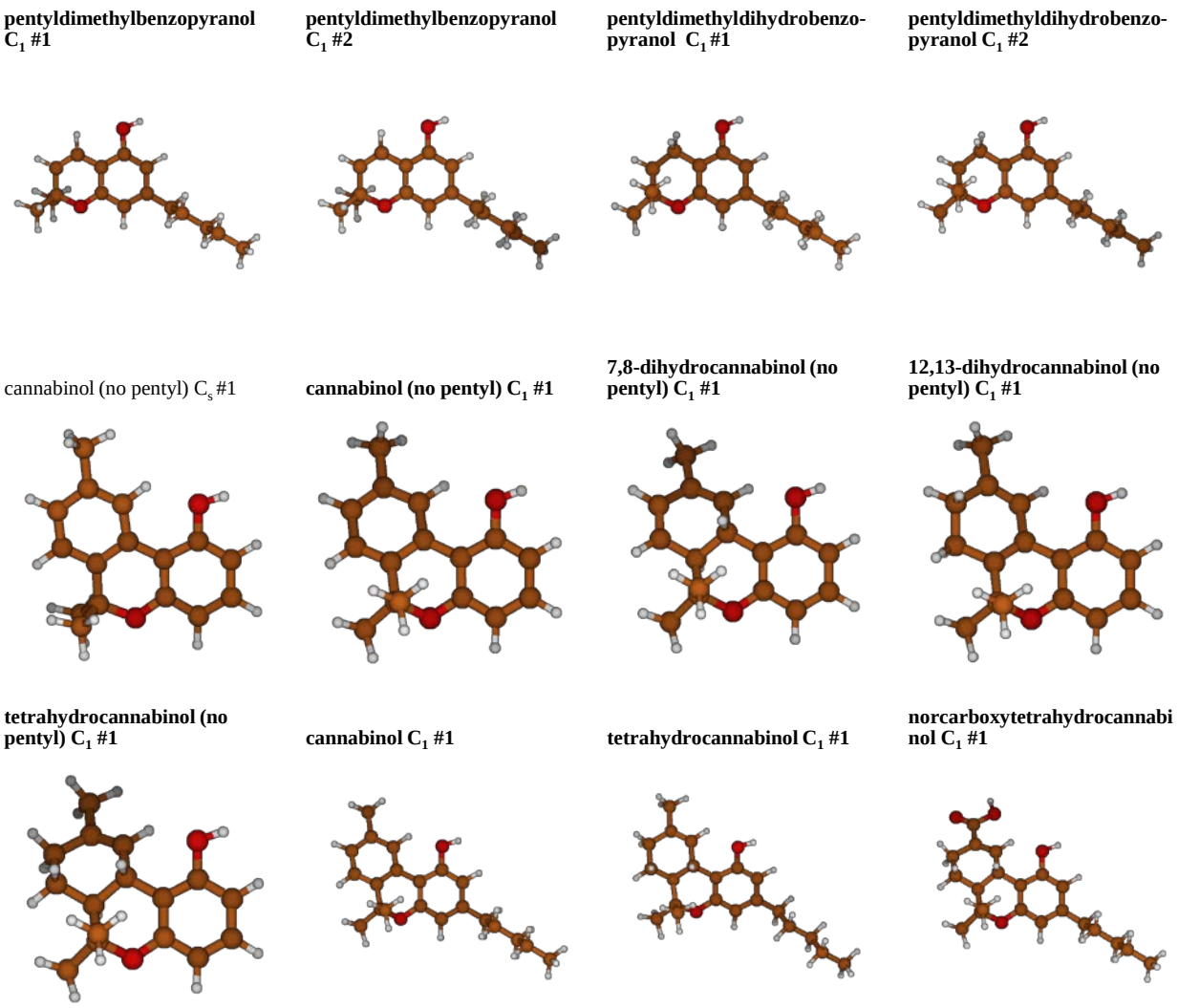

Figure S-1. Model structures examined for computational work

Table 1. Calculated Raman modes for THC and THC-COOH, along with vibrational mode assignment.

Tetrahydrocannabinol (THC)		**11-Nor-9-Carboxy-THC (THC-COOH)**	
Calculated Raman Shift / cm^{-1}	Band Assignment	Calculated Raman Shift / cm^{-1}	Band Assignment
361	OH twist	352	OH twist, mixed
416	Mixed, methyl rock	402	Mixed, methyl rock
442	Mixed, δ(C-C)	444	Mixed, δ(C-C)
474	Mixed, δ(Me-C)	484	Methyl scissor
493	ring def	494	ring def
505	ip def (ring)	504	ip def (ring)
550	ip def (ring)	547	ip def (ring)
577	ip def (ring)	578	OH torsion / carboxyl twist
613	oop def (ring)	616	oop def (ring)
686	ip def (ring)	686	ring def
737	oop def (ring)	736	oop def (ring)
784	CH_2 rock (ring) + CH oop def		
798	CH_2 rock, ν(C-C=C)	794	CH_2 rock, ν(C-C=C)
856	CH oop def (ring) + CH_2 def (chain)		
893	Me rock + CH oop	880	C-O str. (ring)

904	Chain Me rock	903	Chain Me rock
924	CH_2 rock		
946	CH_3 rock, ring def.	941	CH_3 rock, ring def.
1007	CH_3 rock, ν(C-C)	1007	CH_3 rock, ν(C-C)
1013	CH_3 rock, ν(C-C)	1015	CH_3 rock, ν(C-C)
1041	ν(C-C)	1032	CH_3 rock, ν(C-C)
1065	ν(C-C)	1065	ν(C-C)
1108	ν(C-C) ring	1107	ν(C-C)
1127	ν(C-C=C)	1129	ν(C-C=C)
1131	ν(C-C) alkyl chain	1131	ν(C-C) alkyl chain
1176	δ(H-C=C), ν(C-C), CH_3 rock	1181	δ(H-C=C), ν(C-C), CH_3 rock
1206	δ(O-H), ring twist	1209	δ(O-H), ring twist
1239	ν(C-C) ring	1240	mixed, CH ip def + OH def + CC str
1265	CH_2 twist ring	1263	CH_2 twist ring
1311	δ(C-H) (ring junction)	---	---
1344	CH_2 twist chain	1344	CH_2 twist chain
1362	CH_2 twist ring + HCC ip bend	1360	CH_2 twist ring + HCC ip bend+ CC str.
1387	CH_2 wag, δ(=C-H)	1387	CH_2 wag, δ(=C-H)

1401	ip def, coupled to δ(=C-H)	1404	ip def, coupled to δ(=C-H)
1426	$\delta_s(CH_3)$	1421	CH ip bend + CH_2 wag + $\delta_s(CH_3)$
1496	$\delta_s(CH_3)$	1496	$\delta_s(CH_3)$
1507	CH scissor, acyl chain	1508	CH scissor, acyl chain
1517	$\delta_{as}(CH_3)$	1517	δ_{as}(chain CH_3)
1612	ν(C-C=C) localized	1613	ν(C-C=C) localized
1659	ν(C-C=C)	1660	ν(C-C=C)
1719	ν(C=C)	1686	ν(C=C)
---	---	1767	ν(C=O)

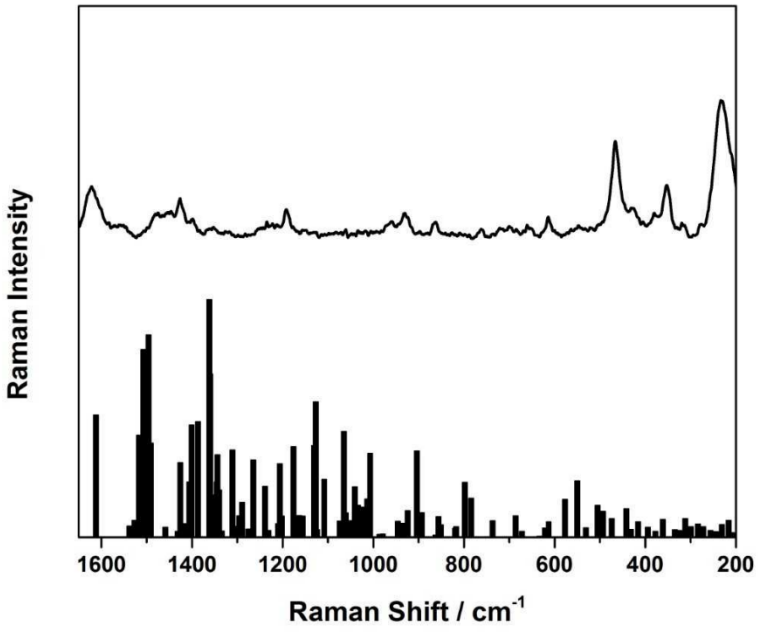

Figure S-2. Comparison of experimental EC-SERS signal obtained for THC at -0.4 V (top) with calculated normal Raman modes for THC using B3LYP/6-31G* level of theory (bottom).

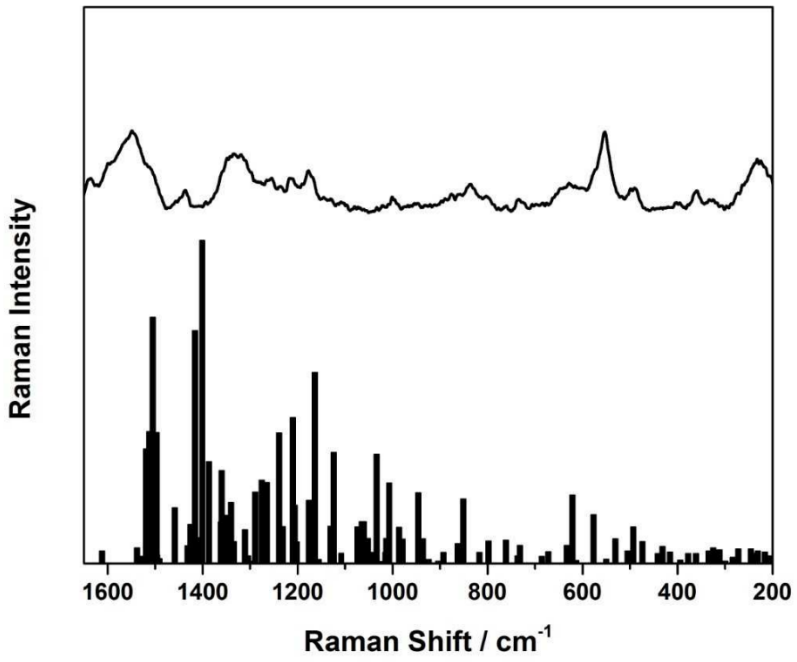

Figure S-3. Comparison of experimental EC-SERS signal obtained for THC-COOH at -0.4 V (top) with calculated normal Raman modes for THC-COOH using B3LYP/6-31G* level of theory (bottom).